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A viral etiology for Ewing's sarcoma

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Summary Despite the finding of characteristic somatic mutations in the tumor tissue and efforts to identify risk factors, the etiology of Ewing's sarcoma (ES) is still unknown. ES is very different from other childhood bone cancers. It rarely occurs in the black population and has no animal model. Recently studies indicate that ES may have a neural, not mesenchymal, origin. It has a distinctive unimodal age-incidence peak at adolescence. Because its incidence curve pattern has a striking resemblance to that of DES-related clear cell adenocarcinoma of the vagina, an in utero exposure might be considered. Although in utero chemical and hormonal exposures have not been found to be associated with ES in epidemiologic studies, we suggest that its etiology could be an in utero viral infection. We hypothesize that the epidemiological characteristics of ES suggest an association with cytomegalovirus (CMV).
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Ewing's sarcoma (ES) is a rare tumor of bone and soft tissue that develops during childhood and adolescence (1). Researchers suspect that it develops from neural tissue (2). Despite continuing efforts to identify possible risk factors, the etiology of ES is unknown. Genetic and environmental factors have been evaluated, but no unifying hypothesis explains the striking epidemiological features of ES. In this paper we review the epidemiology of ES and propose that cytomegalovirus (CMV) may play a role in its development.

EWING'S SARCOMA

Epidemiology

ES is virtually absent in the black population (3). Compiled case series reveal that ES patients are nearly all white (96%) with only 1.8% black and 2.2% of other races (1). Although no marked gender differences are apparent for ES before age 10 or after age 30, males are more frequently affected than females during adolescence. Unlike other bone cancers, there are no animal models (4, and personal communication with Veterinary Medicine Branch, AFIP). Differences in racial distributions and lack of animal models has led to investigations in search of genetic risk factors.

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Genetic factors

Recently, ES was discovered to have a consistent somatic chromosomal translocation, t(11;22)(q24;q12) (5). Many childhood tumors with specific cytogenetic findings have been associated with inherited syndromes or congenital anomalies which have provided insight into the biologic mechanisms of tumor development. Evidence for familial clustering is sparse. ES has been reported in only two pairs of siblings (6,7). Novakovic et al. (8) found an increased risk of stomach and neuroectodermal tumors in relatives of ES patients, but this has not been substantiated by further studies.

One report in the literature cites a case of Down's syndrome with ES (9) and Narod et al. (10) report 2 cases of osteogenic imperfecta. However, other case-control studies have not identified any consistent link with inherited syndromes or medical conditions. There have also been some case reports of skeletal and genitourinary anomalies in patients with ES (11), but the small number of cases may have occurred by chance. Recently, we found an excess number of inguinal hernias in patients treated at the National Cancer Institute Pediatric Branch

(12). These data strengthen the evidence for a consistent association with inguinal hernias, previously reported by others (3,13,14), but the biological basis for this finding remains unclear. Although specific medical conditions have not been consistently found in association with ES, some patients in our NIH study (11) had sensorineural hearing loss years prior to diagnosis. One patient each had prune-belly syndrome, Epstein malformation of the heart, and congenital cataracts.

Environmental factors

In addition to genetic factors, researchers have investigated the possible role of various environmental agents in the development of ES. Although ionizing radiation and alkylating chemotherapeutic drugs are known causes of soft tissue sarcomas and bone cancers, notably osteosarcomas (15), no excess risk has been noted for ES. Two case-control studies reported an increased risk of ES among children whose fathers were employed in agriculture or had pesticide exposure, but subsequent studies reported conflicting results (16–19). Prior studies have also investigated different prenatal risk factors for ES, but without success (16,17,19,20).

Apparently, most patients with ES were normal, healthy newborns and their mothers were in good health during their pregnancies. In an NCI study (11), three mothers of ES patients reported severe illnesses during their pregnancies: one had 'mumps', one had 'German measles' and one had a 'mono-like' illness which resulted in a congenital cataract and opsoclonus in her child. Although most studies have been negative for in utero exposures, the theory that an intrauterine exposure to an environmental agent might subsequently lead to cancer in teenage years would be a good model for ES. This latency pattern has been seen before with clear cell vaginal adenocarcinoma due to an in utero exposure to diethylstilbesterol (DES) (21). Both these tumors have a characteristic unimodal age peak during adolescence, rarely occurring before age 3 or after age 30. Although no chemical agents or maternal medications have been consistently linked to ES, infectious agents have been less well studied.

Infectious agents

In Sweden, 1974, Larsson et al. did not find any temporal-spatial variation of Ewing's sarcoma to suggest an infectious cause (22). However, the hypothesis that ES is caused by an oncogenic virus of farm animals was postulated in the reports of ES in six individuals living in rural area of Australia (23) and two brothers living in rural Spain (24). Daurgaard et al. (25) proposed that EBV might be associated with ES, but they were unable to detect viral DNA in tumor tissues from seven patients with the disease. We are considering a viral etiology for ES for several reasons.

Viruses seem to be involved in about 15% of all cancers (26). Burkitt's lymphoma, Kaposi's sarcoma, cervical cancer and hepatocellular carcinoma have all been linked to viruses. Of all possible cancer-causing viruses, the herpesviruses are known for their oncogenic potential Tying together information from case reports, case series, population studies, and case-control studies, we propose that the oncogenic herpesvirus CMV could be causally linked to the development of ES.

Cytomegalovirus

CMV is a herpesvirus. The herpesvirus family is well known for its oncogenic potential. Herpesviruses infect lymphoid cells. They can persist in a latent stage and reactivate at a later time. Currently CMV is not known to be associated with any cancers, but it has been investigated as the causal agent of several, including Kaposi's sarcoma (27).

CMV is the most common virus associated with congenital and perinatal infections, affecting 1% of newborns worldwide (28). Primary and secondary infections in both pregnant women and infants typically are asymptomatic. If a pregnant woman were symptomatic, her illness might resemble that of infectious mononucleosis or hepatitis. As in other intrauterine infections, severely affected infants are born premature. These infants may have features of hepatosplenomegaly, intrauterine growth retardation, seizures, hydrocephalus, and platelet abnormalities. Rare, but clinically striking cases may also have either congenital cataracts or a type of eye movement disorder, optikinetic ophthalmus. No evidence indicates that CMV is teratogenic (causing major organ malformations). CMV has been associated, however, with inguinal hernias, tooth enamel defects, and first branchial arch anomalies, and other congenital anomalies (29–31). Inguinal hernias associated with CMV have been reported in sets of siblings (32,33). A recent case report suggested that CMV had induced prune-belly syndrome in two infants (34). The most common handicap caused by congenital CMV infection is a permanent sensorineural hearing loss that usually is not detected until late childhood (30). Congenital CMV also may cause bone defects, including rarefaction of the long bones, especially the femur and tibia (35). Rarey et al. (36) reported that extensive bone damage following congenital CMV was still evident 14 years after birth.

A viral hypothesis for Ewing's sarcoma

We hypothesize that ES may be causally related to an in utero infection with CMV. The infection is a common

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Table 1 Features of congenital CMV and Ewing's sarcoma

	Congenital CMV	Ewing's sarcoma
Racial distribution	White infants, rare in blacks	White, rare in blacks
Age distribution	Primary infection or reactivation of latent infection in mother	Adolescence
Animal model	Human species-specific	Humans only
Target tissues	Nervous system	Neural (postulated)
Reported anomalies	Inguinal hernia	Inguinal hernia (4 studies)
	Cataract	Cataract (2 studies)
	Microphthalmia, strabismus	Microphthalmia, strabismus (1 study)
	CNS anomalies	Microcephaly, serizures, hydrocephalus (1 study)
	Sensorineural hearing loss*	Sensorineural hearing loss (1 study)
	Bone lesions (rarefaction of long bones, skull densities)	Bone lesions–dysplasias, bone cysts (3 studies)
	Intrauterine growth retardation	Low birth weight (1 study)
	Cardiac defects	
		Genitourinary defects cryptorchidism (2 studies)

* Most common manifestation of congenital CMV (31).

one; ES could be a rare sequel. The association would be similar to the association of an intrauterine exposure to DES with the rare outcome of adenocarcinoma of the vagina arising in adolescence. Both tumors peak at adolescence.

CMV and ES share three main epidemiological features: (A) Humans appear to be the only hosts for CMV. ES occurs only in humans, species-specific. (B) Severe primary congenital CMV infections are more likely to occur in white infants than in black infants. Black and Asian populations acquire CMV immunity at very young ages, while whites acquire immunity much later. Seropositivity for CMV is high among pregnant black women and low among pregnant white women. Therefore, white infants are more likely to have severe primary infections due to the lack of passive immunity from their mothers. This agrees with the finding that ES is virtually non-existent in blacks (3). (C) CMV affects mostly neural tissues. Although congenital CMV may cause multi-system disease, the most frequent disease appears in the nervous system. This would be consistent with a neural origin for ES. In addition CMV affects bone tissue, the usual site of ES. Inguinal hernias associated with CMV have been found in more than one child in the family and this has also been reported for ES.

Other rare but striking clinical features of congenital CMV were observed in some of our patients who had ES. These include inguinal hernias in both female and male patients, sensorineural hearing loss, prune-belly syndrome, and congenital cataracts. Together, they might provide supportive evidence for a role of CMV in ES. For such a devastating disease, and with so few etiological leads to follow, we feel that this hypothesis for ES warrants further study with viral testing of tumor tissue for CMV.

REFERENCES

1. Horowitz M. E., Malawer M. M., Woo S. Y., Hicks M. J. Ewing's sarcoma family of tumors: Ewing's sarcoma of bone and soft tissue and the peripheral primitive neuroectodermal tumors. In: Pizzo P. A, Poplack D. G., eds. Principles and Practice of Pediatric Oncology, 3rd edn. Philadelphia: Lippincott-Raven 1997: 831–864.
2. Cavazzana A. O., Miser J. S., Jefferson J., Triche T. J. Experimental evidence for a neural origin of Ewing's sarcoma of bone. *Am J Pathol* 1987; **127**: 507–518.
3. Glass A. G., Fraumeni J. F. Epidemiology of bone cancer in children. *JNCI* 1970; **44**(1): 187–199.
4. Miller R. W. Etiology of childhood bone cancer epidemiological observations. *Recent Results Cancer Res* 1976; **54**: 50–62.
5. Barr F. G., Chatten J., D'Cruz C. M. et al. Molecular assays for chromosomal translocations in the diagnosis of pediatric soft tissue sarcomas. *JAMA* 1995; **273**(7): 553–557.
6. Hutter R. V. P., Francis K. C., Foote F. W. Jr. Ewing's sarcoma in siblings. Report of the second known occurrence. *Am J Surg* 1964; **107**: 598–603.
7. Joyce M. J., Harmon D. C., Mankin H. J., Suit H. D., Schiller A. L., Truman J. T. Ewing's sarcoma in female siblings: A clinical report and review of the literature. *Cancer* 1983; **53**: 1959–1962.
8. Novakovic B. Increased risk of neuroectodermal tumors and stomach cancer in relatives of patients with Ewing's sarcoma family of tumors. *J Natl Cancer Inst* 1994; **86**(22): 1702–1706.
9. Casorzo L., Fessia L., Sapino A., Ponzio G., Bussolati G. Extraskeletal Ewing's tumor with translocation t(11;22) in a patient with Down syndrome. *Cancer Genet Cytogenet* 1989; **37**: 79–84.
10. Narod S. A., Hawkins M. M., Robertson C. M., Stiller C. A. Congenital anomalies and childhood cancer in Great Britain. *Am J Hum Genet* 1997; **60**: 474–485.
11. McKeen E. A., Hanson M. R., Mulvihill J. J. Glaubiger D. L. Birth defects with Ewing's sarcoma. *N Engl J Med* 1983; **309**: 1522.
12. Cope J. U., Tsokos M. G., Helman L. J., Gridley G., Tucker M. A. Inguinal hernia in patients with Ewing's sarcoma – a clue to etiology. Med Ped Oncol 2000; **34**: 195–199.
13. Bacci G., Gerrari S., Rosito P. et al. Ewing's sarcoma of the bone. Anatomoclinical study of 424 cases. *Minerva Pediatr* 1992; **44** (7–8): 345–359.

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14. Li P. P., Jamison D. S., Meadows A. T. Questionnaire study of cancer etiology in 503 children. *J Natl Cancer Inst* 1986; **76**(1): 31–36.
15. Tucker M. A., D'Angio G. J., Boice J. D. et al. Bone sarcomas linked to radiotherapy and chemotherapy in children. *N Engl J Med* 1987; **317**: 588–593.
16. Buckley J. D., Pendergrass T. W., Buckley C. M. et al. Epidemiology of osteogenic sarcoma and Ewing's sarcoma: a study of 305 cases by the Children's Cancer Group. *Cancer* 1998; **83**(7): 1440–1448.
17. Holly E. A., Aston D. A., Ahn D. K., Kristiansen J. J. Ewing's bone sarcoma, paternal occupational exposure, and other factors. *Am J Epidemiol* 1996; **135**: 122–129.
18. Hum L., Krieger N., Finkelstein M. M. The relationship between parental occupation and bone cancer risk in offspring. *Int J Epidemiol* 1998; **27**: 766–771.
19. Winn D. M., Li F. P., Robison L. L., Mulvihill J. J., Daigle A. E., Fraumeni J. F. Jr. A case-control study of the etiology of Ewing's sarcoma. *Cancer Epidemiol Biomarkers Prev* 1992; **1**(7): 525–532.
20. Hartley A. L., Birch J. M., McKinney P. A. et al. The Inter-Regional Epidemiological Study of Childhood Cancer (IRESCC): case-control study of children with bone and soft tissue sarcomas. *Br J Cancer* 1988; **58**: 838–842.
21. Herbst A. L., Ulfelder H., Poskanzer D. C. Association of maternal stilbesterol therapy with tumor appearance in your women. *N Engl J Med* 1971; **248**: 878–881.
22. Larsson S., Lorentzon R. The geographic variation of the incidence of malignant primary bone tumors in Sweden. *J Bone Joint Surg* 1974; **56**-A: 592–600.
23. Holman C. D. J., Reynolds P. M., Byrne M. J. J., Trotter J. M., Armstrong B. K. Possible infectious etiology of six cases of Ewing's sarcoma in Western Australia. *Cancer* 1983; **52**: 1974–1976.
24. Zamora P., Garcia de Paredes M. L., Baron M. G. et al. Ewing's tumor in brothers. *Am J Clin Oncol* 1986; **9**: 358–360.
25. Daugaard S., Hording U., Schiodt T. Ewing's sarcoma and Epstein–Barr virus. *Eur J Cancer* 1991; **27**: 1334.
26. zur Hausen H. Viruses in human cancers. *Science* 1991; **254**: 1167–1173.
27. Giraldo G., Beth E., Huang E.-S. Kaposi's sarcoma and its relationship to cytomegalovirus (CMV): III. CMV DNA and CMV early antigens in Kaposi's sarcoma. *Int J Cancer* 1980; **26**: 23–29.
28. Alford C. A., Stagno S., Pass R. F., Britt W. J. Congenital and perinatal CMV infections. *Rev Infect Dis* 1990; Suppl **7**: S745–753.
29. Gold E., Nankervis G. A. Cytomegalovirus. In: Evans A.S. Viral Infections of Humans, 2nd edn. New York: Plenum, 1982; 167–186.
30. Merigan T. C., Resta S. Cytomegalovirus: Where have we been and where are we going? *Rev Infect Dis* 1990; Suppl **7**: S693–700.
31. Stagno S. Cytomegalovirus In: Remington J. S., Klein J. O. Infectious Diseases of the Fetus and Newborn Infant, 4th edn. Philadelphia, PA: WB Saunders, 1995: 312–353.
32. Hardy J. R., Sever J. L. Indirect inguinal hernia in congenital rubella. *J Pediatr* 1968; **73** Sept: 9416–9418.
33. Lang D. J. The association of indirect inguinal hernia with congenital cytomegalic inclusion disease. *Pediatrics* 1966; **38**: 913.
34. Donnelly L. F., Johnson J. F. III. Unilateral abdominal wall hypopolasia: radiographic findings in two infant girls. *Pediatr Radiol* 1995; **25**: 278–279.
35. Alessandri J. L., Breton A., Montbrun A., Bratzlawsky C., Tuaillon J., Tilmont P. Bone abnormalities and fetal cytomegalovirus infection. *Arch Pediatr* 1995; **2**: 650–653.
36. Rarey K. E., Davis L. E. Temporal bone histopathology 14 years after cytomegalic inclusion disease: a case study. *Laryngoscope* 1993; **103**: 904–909.

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